REMARKS

Claims 1-8 are pending.

Support for Amendments

Claim 1 is amended to remove the phrase "or prodrugs" from the claim. Claim 5 is amended to remove trademarks and duplicative entries. Applicants reserve the right to pursue any canceled subject matter in one or more continuing applications. Support can be found throughout the specification as filed. No new matter is added.

Rejection Under 35 U.S.C. § 112, 1st paragraph

Claims 1-8 are rejected under 35 U.S.C. § 112, 1st paragraph, as failing to comply with the written description requirement. The Office Action asserts that the specification fails to comply with the written description requirement due to the term "prodrugs." Applicants respectfully traverse. Nevertheless, in order to advance prosecution, the phrase "or prodrugs" is deleted from claim 1. Applicants respectfully request withdrawal of the rejection as moot.

Rejection Under 35 U.S.C. § 112, 2nd paragraph

Claim 5 is rejected under 35 U.S.C. § 112, 2nd paragraph, as being indefinite due to the inclusion of trademarks in the claims. The Office Action suggests that the rejection can be obviated by removal of the trademarks. Upon entry of this paper, claim 5 is amended to remove trademarks and duplicative terms. Applicants respectfully request withdrawal of the rejection.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Schinazi et al (U.S. Patent No. 5,703,058, referred to as "Schinazi '058") and Thyagarajan (U.S. Patent No. 6,589,570). Applicants respectfully request clarification as to the date which is relied upon for establishing Thyagarajan as prior art. In any event, Applicants respectfully traverse the rejection for reasons as discussed below.

The Office Action Fails to Meet the Legal Standard for Obviousness

Recently, the Supreme Court reviewed the legal standard for obviousness in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). In *KSR*, the Supreme Court reaffirmed its prior holding that the obviousness analysis requires that "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *Id.*, at 1734 (citing *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966)). While the Supreme Court found the particular claimed structure in *KSR* to be obvious, the Court pointedly noted that, consistent with a broad body of patent law, "**a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art**." *KSR*, 127 S. Ct., at 1741 (emphasis added). Rather, to determine whether the differences between the art and the claims would have been obvious, the Court mandated analytical flexibility, leaving intact the Federal Circuit's teaching-suggestion-motivation ("TSM") test, while permitting the "obvious to try" doctrine under certain limited circumstances.

In a series of three recent opinions, the Federal Circuit declined to apply the "obvious to try" standard of *KSR* in drug cases involving unpredictable solutions, finding the TSM test to be more appropriate. See *Takeda Chemical Indus. v. Alphapharm*, 492 F.3d 1350 (Fed. Cir. 2007); *Ortho–McNeil Pharma. v. Mylan Labs.*, 520 F.3d 1358 (Fed. Cir. 2008); and *Eisai Co. v. Dr. Reddy's Labs.* (Fed. Cir. 2008). Specifically, in *Takeda*, the lack of a finite number of identified and predictable solutions led the Court to state "this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was 'obvious to try.'" *Takeda*, at 1359. Similarly, in *Eisai*, the Court cautioned that, "[t]o the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."

The Office Action provides no evidence in support of predictability for anti-HBV treatments. Rather, the Office Action asserts that "[o]ne of ordinary skill in the art could have combined the elements as claimed by known methods and that in combination, each element merely would have performed the same function as it did separately, to treat or prophylax against HBV" (p. 6, lines 18-20). The Examiner appears to be taking the exact position that the Supreme Court warned against when it said that "**a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art**." *KSR*, 127 S. Ct., at 1741 (emphasis added). Essentially, the Examiner's suggestion that one can simply administer three pharmaceutically active compounds and have a reasonable expectation that the combination would be successful ignores the fact that drugs may be inactive or have drug-drug interactions (causing untoward side effects) if combined. As such, the Federal Circuit's recent holdings in *Takeda*, *Ortho-McNeil*, and *Eisai*, as discussed above,

clearly support the non-obviousness of Applicants' invention, at least because of a lack of a small, finite number of identified, predictable solutions. For at least this reason, Applicants request withdrawal of the rejection.

The Office Action Mischaracterizes the Teachings of the Cited Art

The Office Action states that Schinazi '058 teaches that FTC exhibits activity against Hepatitis B Virus (col. 2, lines 40-41), that alpha interferon is effective for HBV (col. 2, lines 46-55), and that L-FMAU is an example of an antiviral agent that can be used in combination with the (-) enantiomer of FTC (col. 6, lines 21-27) for the treatment of HBV infections in humans (col. 3, lines 5-6). See Office Action, p. 6, lines 5-10 and 14-17, and p. 9, lines 15-19. Applicants respectfully disagree with this characterization of Schinazi '058 as provided in the Office Action.

Schinazi '058 does not teach that "L-FMAU is an example of an antiviral agent that can be used in combination with the (-) enantiomer of FTC" as characterized by the Office Action. Rather, Schinazi '058 exactly states the following:

> Nonlimiting examples of antiviral agents that can be used in combination with the compounds disclosed herein include the (-)-enantiomer of 2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC); the (-)-enantiomer of 2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC); carbovir, acyclovir, interferon, famciclovir, penciclovir, AZT, DDI, DDC, L-(-)-FMAU, and D4T.

(col. 6, lines 21-27). The cited passage clearly does not teach the combination of the (-) enantiomer of FTC with L-FMAU. A plain reading of the passage clearly shows that either the (-) enantiomer of FTC or L-FMAU (or any one of the other 10 compounds listed in the passage) can be combined with the genus of thousands of compounds presented from col. 3, line 20

through col. 6, line 3. Any reason to combine the (-) enantiomer of FTC with L-FMAU is supplied entirely and improperly by the Examiner, and not by Schinazi '058.

Moreover, Schinazi does not teach that alpha interferon is effective for HBV as characterized by the Examiner; rather, Schinazi '058 states that "[d]aily treatments with α-interferon, a genetically engineered protein, has also shown promise," (col. 2, lines 54-55). The remaining passage cited by the Office Action, *i.e.*, col. 2, lines 45-52, is directed to a vaccine derived from human serum used to immunize patients against HBV, and is entirely unrelated to alpha interferon.[1] Applicants assert that the statement from Schinazi '058 related to alpha interferon (*i.e.*, col. 2, lines 54-55) is not evidence of effectiveness of treatment of HBV with alpha interferon, but rather mere conjecture on the part of Schinazi '058 without support of any data or other indicia of reliability. Moreover, one of ordinary skill in the art would recognize the statement from Schinazi '058 at col. 2, lines 54-55 provides no data for one of ordinary skill in the art to evaluate, and therefore, one of ordinary skill in the art would not rely on such a statement as evidence of effectiveness of alpha interferon in treating HBV.

The Office Action argues that regarding the substantially pure form of β-L-FTC, Schinazi '058 teaches that the β-L forms are specifically contemplated (column 7, line 64 to column 8, line 3). Applicants note that the passage cited by the Office Action states

> The antivirally active compounds disclosed herein are [5-carboxamido or 5-fluoro]-2',3'-dideoxy-2',3'-didehydro-pyrimidine nucleosides and [5-carboxamido or 5-fluoro]-3'-modified-pyrimidine nucleosides, in the racemic or β-D or β-L enantiomerically enriched form.

[1] A more detailed description of the human serum-derived vaccine can be found in Lau, cited in the previous IDS and considered by the Examiner on Sept. 23, 2008, at page S53, right column, lines 44-67, which clearly shows that the reference to human serum-derived vaccine by Schinazi does not refer to interferons.

(Schinazi '058, column 7, line 64 to column 8, line 3). In this passage, Schinazi '058 is actually discussing the inventive compounds discussed at columns 3, 4, and 5, rather than the other non-inventive antiviral agents (*i.e.*, FTC and other compounds) described separately by Schinazi '058 at column 6, lines 21-27.

With respect to Thyagarajan, the Office Action states that Thyagarajan recites in Table 1 (column 2) agents that have been studied and "are successful" in the treatment of HBV infection, including interferons such as alpha interferon, beta interferon, and gamma interferon. See Office Action, page 8, lines 18-22. Applicants note that Thyagarajan does not state that the interferons are successful in the treatment of HBV infection. The finding that interferons are successful in the treatment of HBV infection is improperly supplied by the Examiner, and not by Thyagarajan. Rather, Thyagarajan states that interferons are agents "that have been studied in the treatment of HBV infection" (see Table 1 heading, emphasis added). The act of studying an agent does not suggest to one of ordinary skill in the art that the agent is therefore successful. In fact, Thyagarajan states that the interferons have limited success (*i.e.*, are not successful), prohibitive costs, profound side effects, and are non-accessible. See col. 2, lines 42-46. One of ordinary skill in the art would recognize the teachings of Thyagarajan as teaching away from the use of interferons, as Thyagarajan specifically teaches that the above-recited negative qualities of interferons "have necessitated further search for newer antihepatitis B agents" (col. 2, lines 45-46).

Clearly, the Office Action's reliance on Thyagarajan as teaching that interferons "are successful" in the treatment of HBV is a mischaracterization of Thyagarajan, and does not consider the teachings of Thyagarajan as a whole. Notably, Lau (cited in the previous IDS and considered by the Examiner on Sept. 23, 2008) is the source from which Thyagarajan took Table

I (see Lau, p. S54, left column, Table III). Lau teaches that "a series of trials were conducted in the search for alternative therapeutic agents (Table III)" where Table III includes alpha, beta, and gamma interferons, and that the trials "provided a clear negative result" (Lau, p. S54, left column, lines 13-17). When taken as a whole, the Thyagarajan reference relied upon by the Office Action teaches away from the use of interferons individually, and provides no motivation whatsoever to add interferons to other combinations. In fact, Thyagarajan specifically teaches that such compounds should not be used, but rather newer antihepatitis B agents should be developed (see col. 2, lines 44-46).

The Office Action Fails to Provide Motivation for Administration of Three Components

The Office Action argues that the motivation for administering ß-L-FTC, L-FMAU, and interferon is one of "great convenience" (p. 7, line 3), and that the selection of a known material based on its suitability for its intended use supports an obviousness determination, citing *Sinclair & Carroll Co. v. Interchemical Corp.* (p. 7, lines 5-7, and p. 10, lines 3-5). Applicants note that neither of the cited references teaches the "great convenience" of administering ß-L-FTC, L-FMAU, and interferon. Moreover, the Supreme Court has specifically stated that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 127 S. Ct., at 1741. The Office Action fails to provide any motivation (or reason) why one of ordinary skill in the art would specifically look to ß-L-FTC, L-FMAU, and interferon for administration together from among the universe of possible active agents. Rather, the Office Action can only arrive at the specifically claimed three components through hindsight reconstruction of Applicants' own

invention, which is improper. For at least this reason, Applicants request withdrawal of the rejection.

The Cited References Fail to Provide a Reasonable Expectation of Success

The Office Action provides no evidence in support of predictability for anti-HBV treatments, or any basis from the technical literature for a reasonable expectation of success. Rather, the Office Action asserts that "[o]ne of ordinary skill in the art could have combined the elements as claimed by known methods and that in combination, each element merely would have performed the same function as it did separately, to treat or prophylax against HBV" (p. 6, lines 18-20). Yet there is simply no support in the references cited by the Office Action to arrive at the general rule that would suggest to one of ordinary skill in the art that one can randomly combine three anti-HBV agents with an expectation of success.

In fact, Applicants note that the scientific literature actually discloses the difficulty of arriving at successful combination therapy. For example, Osborn ("Antiviral options for the treatment of chronic hepatitis B," Journal of Antimicrobial Chemotherapy, vol. 57, p. 1030-1034, April 4, 2006, cited on the accompanying IDS) discloses that "[t]heoretically, combination therapy should have additive or synergistic antiviral activity, and prevent or reduce drug resistance," (p. 1033, left column, lines 23-24). Yet, in reality, tests of actual compounds found combination therapy inferior to treatment with one agent alone, thus "suggesting an antagonistic effect" (p. 1033, left column, lines 34-36). Thus, Osborn reviews actual data, and finds that "the promise of combination therapy remains elusive for hepatitis B" (p. 1033, left column, lines 36-37).

Applicants note that all evidence of nonobviousness must be considered when assessing patentability. See *In re Sullivan*, 498 F.3d 1345, 1351 (Fed. Cir. 2007), citing *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) and *In re Sernaker*, 702 F.2d 989, 996 (Fed. Cir. 1983). Applicants have provided evidence from the literature that success in combining even two anti-HBV agents "remains elusive" (see Osborn, page 1033, left column, lines 36-37), and respectfully submit that the evidence of actual failure provided by Applicants outweighs the unsupported assertion in the Office Action that "each element merely would have performed the same function as it did separately, to treat or prophylax against HBV" (p. 6, lines 18-20). Indeed, the Federal Circuit has held that "there can be little better evidence negating an expectation of success than actual reports of failure." See *Boehringer Ingelheim Vetmedica v Schering-Plough Corporation*, 320 F.3d 1339, 1354 (Fed. Cir. 2003), citing *In re Rinehart*, 531 F.2d 1048, 1053-54 (CCPA 1976).

The Office Action Applies Case Law That Is Not Relevant To Obviousness

The Office Action acknowledges Applicants' previous argument that Thyagarajan teaches that interferons have a limited success rate, prohibitive cost, and profound side effects, as well as being non-accessible. The Office Action responds that "it is immaterial whether it has prohibitive cost, profound side effects or it is non-accessible" (p. 10, lines 15-16). In support of this position, the Office Action cites *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994), stating that "therapeutic utility sufficient under patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs" (p. 10, lines 16-20). The Office Action further states that usefulness includes the expectation of further research and development., and that "Title 35 does not require Phase II testing in order to prove utility," (p. 11, lines 1-3).

While the case law cited in the Office Action is relevant to utility (35 U.S.C. § 101), Applicants note that the present rejection is based on obviousness (35 U.S.C. § 103) rather than utility (35 U.S.C. § 101). Applicants can find nothing in the MPEP or the case law that suggests that the Federal Circuit holdings with regard to utility under 35 U.S.C. § 101 can or should be applied by Examiners to obviousness under 35 U.S.C. § 103. Simply put, the two legal standards are separate, and the case law cited by the Examiner is entirely irrelevant to the question at hand, which is whether or not the claimed methods are obvious. In that respect, the prohibitive cost, profound side effects, and inaccessibility of interferons is completely material to the question of whether or not it would be obvious for one of ordinary skill in the art to administer interferon with β-FTC and L-FMAU in a treatment for hepatitis B as claimed. As noted at MPEP 2141.02VI, a prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). Case law directed to utility notwithstanding, there is no basis for the Examiner to ignore the teachings of Thyagarajan regarding the deficiencies of interferons.

In summary, the cited references provide no motivation to administer the three active ingredients, and no expectation of success with respect to the claimed administration of three anti-HBV agents. To the contrary, Applicants have provided evidence of failure in the literature which negates any expectation of success. Moreover, the Office Action mischaracterizes the teachings of the cited references, relies on case law that is not relevant to obviousness, and fails to meet the legal standard for obviousness. For all of these reasons, Applicants respectfully request withdrawal of the rejection.

Having distinguished the independent claim from the art of record, Applicants submit that the claims dependent therefrom are patentable for at least the same reasons. However, Applicants reserve the right to separately address the patentability of those claims in the future should that become necessary.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 04674.105074 (TRI 1016).

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 04674.105074 (TRI 1016).

Respectfully submitted,
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